JC10 Rec'd PCT/PTO 08 JAN 2002

FORM PTO-1390 REV. 2/01T — U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37CFR1.5)
03715.0103	10/030262

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR00/01971	July 7, 2000	July 9, 1999

TITLE OF INVENTION
PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND METHOD FOR THE PREPARATION THEREOF

APPLICANT(S) FOR DO/EO/US
Bruno CRIERE, Pascal SUPLIE, and Philippe CHENEVIER

Applicant(s) herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c)(2)).
   - a. ☐ is attached hereto (required only if not communicated by the International Bureau.
   - b. ☒ has been communicated by the International Bureau.
   - c. ☐ is not required, as the application was filed with the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
   - a. ☒ is attached hereto.
   - b. ☐ has been previously submitted under 35 U.S.C. 154 (d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3)).
   - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   - b. ☐ have been communicated by the International Bureau.
   - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☒ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ Information Disclosure Statement under 37 CFR 1.97 and 1.98
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A Substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154 (d)(4).
19. ☐ A second copy of the English language translation of the international application 35 U.S.C. 154 (d)(4).
20. ☒ Other items or information:
    - a. ☒ Copy of cover page of International Publication No. WO 01/03693
    - b. ☐ Copy of Notification of Missing Requirements.
    - c. ☐

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U.S. APPLICATION NO. (If known, see 37CFR 1.5) 10/030262	INTERNATIONAL APPLICATION NO. PCT/FR00/01971	ATTORNEY'S DOCKET NUMBER 03715.0103

21. ☒ The following fees are submitted:

CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTOand all claims satisfied provisions of PCT Article 33 (1)-(4) **$100.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =				$890.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).				$	
CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	
Total Claims	15	- 20 =		x $18.00	$
Independent Claims	1	-3 =		x $84.00	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+$280.00	$280.00
TOTAL OF THE ABOVE CALCULATIONS =				$1170.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.				$	
SUBTOTAL =				$1170.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				1170.00	
Fee for recording the enclosed assignment (37 CFR 1.21 (h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property. +				$	
TOTAL FEES ENCLOSED =				$1170.00	
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $ 1170.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-0916. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

DATED: January 8, 2002

SIGNATURE

Ernest F. Chapman Reg. No. 25,961

NAME/REGISTRATION NO.

10/030262
JC13 Rec'd PCT/PTO 08 JAN 2002

PATENT
Attorney Docket No. 03715.0103
CUSTOMER NUMBER 22,852

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#3/a

In re U.S. national phase of PCT/FR00/01971:

Inventors: Bruno CRIERE et al.

Serial No.: Not Yet Assigned

Filed: January 8, 2002

For: PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND METHOD FOR THE PREPARATION THEREOF

Group Art Unit:

Examiner:

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

Prior to examination, please amend the above-identified application as follows:

IN THE SPECIFICATION:

Please substitute lines 17-25 on page 10 of the specification with the following:

The following abbreviations are used in the present application:

C_{max}: maximum concentration in the plasma,

T_{max}: time required to attain the Cmax,

$Elim_{1/2}$: plasmatic half-life,

AUC_{0-t}: area under the curve from 0 to t,

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$AUC_{0-\infty}$: area under the curve from 0 to ∞,

Ke: Elimination constant.

REMARKS

The above-identified application has been amended to correct a minor typographical error in the specification. No new matter has been introduced by the amendment. An amended form of lines 17-25 is attached for the Examiner's convenience pursuant to new rule 37 C.F.R. §1.21(c)(1)(ii). This paper is not intended to be entered.

The examiner is respectfully requested to consider the above preliminary amendment prior to examination of the application.

If there are any other fees due in connection with the filing of this response, please charge the fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: January 8, 2002

By: _____
Ernest F. Chapman
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EFC/FPD/gah

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APPENDIX TO PRELIMINARY AMENDMENT OF JANUARY 8, 2002

Please amend page 10, lines 17-25 of the specification as follows:

The following abbreviations are used in the present application:

C_{max}: maximum concentration in the plasma,
T_{max}: time required to attain the Cmax,
[T] Elim $_{1/2}$: plasmatic half-life,
AUC_{0-t}: area under the curve from 0 to t,
$AUC_{0-\infty}$: area under the curve from 0 to ∞,
Ke: Elimination constant.

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10/030262
JC13 Rec'd PCT/PTO 08 JAN 2002

"Pharmaceutical composition containing fenofibrate and method for the preparation thereof"

The present invention relates to a novel pharmaceutical composition containing fenofibrate.

Fenofibrate is recommended in the treatment of adult endogenous hyperlipidemias, of hypercholesterolemias and of hypertriglyceridemias. A treatment of 300 to 400 mg of fenofibrate per day enables a 20 to 25% reduction of cholesterolemia and a 40 to 50% reduction of triglyceridemia to be obtained.

The major fenofibrate metabolite in the plasma is fenofibric acid. The half-life for elimination of fenofibric acid from the plasma is of the order of 20 hours. Its maximum concentration in the plasma is attained, on average, five hours after ingestion of the medicinal product. The mean concentration in the plasma is of the order of 15 micrograms/ml for a dose of 300 mg of fenofibrate per day. This level is stable throughout treatment.

Fenofibrate is an active principle which is very poorly soluble in water, and the absorption of which in the digestive tract is limited. An increase in its solubility or in its rate of solubilization leads to better digestive absorption.

Various approaches have been explored in order to increase the rate of solubilization of fenofibrate: micronization of the active principle, addition of a surfactant, and comicronization of fenofibrate with a surfactant.

Patent EP 256 933 describes fenofibrate granules in which the fenofibrate is micronized in order to increase its bioavailability. The crystalline

fenofibrate microparticles are less than 50 µm in size. the binder used is polyvinylpyrrolidone. The document suggests other types of binder, such as methacrylic polymers, cellulose derivatives and polyethylene glycols. The granules described in the examples of EP 256 933 are obtained by a method using organic solvents.

Patent EP 330 532 proposes improving the bioavailability of fenofibrate by comicronizing it with a surfactant, such as sodium lauryl sulfate. The comicronizate is then granulated by wet granulation in order to improve the flow capacities of the powder and to facilitate the transformation into gelatin capsules. This comicronization allows a significant increase in the bioavailability compared to the use of fenofibrate described in EP 256 933. The granules described in EP 330 532 contain polyvinylpyrrolidone as a binder.

This patent teaches that the comicronization of fenofibrate with a solid surfactant significantly improves the bioavailability of the fenofibrate compared to the use of a surfactant, of micronization or of the combination of a surfactant and of micronized fenofibrate.

Patent WO 98/31361 proposes improving the bioavailability of the fenofibrate by attaching to a hydrodispersible inert support micronized fenofibrate, a hydrophilic polymer and, optionally, a surfactant. The hydrophilic polymer, identified as polyvinyl-pyrrolidone, represents at least 20% by weight of the composition described above.

This method makes it possible to increase the rate of dissolution of the fenofibrate, and also its bioavailability. However, the preparation method according to that patent is not entirely satisfactory since it requires the use of a considerable amount of

PVP and of the other excipients. The example presented in that patent application refers to a composition containing only 17.7% of fenofibrate expressed as a mass ratio. This low mass ratio for fenofibrate leads to a final form which is very large in size, hence a difficulty in administering the desired dose of fenofibrate, or the administration of two tablets.

In the context of the present invention, it has been discovered that the incorporation of a cellulose derivative, used as a binder and solubilization adjuvant, into a composition containing micronized fenofibrate and a surfactant makes it possible to obtain a bioavailability which is greater than for a composition containing a comicronizate of fenofibrate and of a surfactant.

A subject of the present invention is therefore a pharmaceutical composition containing micronized fenofibrate, a surfactant and a binding cellulose derivative, which is a solubilization adjuvant, preferably hydroxypropylmethylcellulose (HPMC).

The composition of the invention is advantageously provided as gelatin capsules containing powder or granules, preferably in the form of granules. These granules may in particular be prepared by assembly on neutral microgranules, by spraying an aqueous solution containing the surfactant, the solubilized binding cellulose derivative and the micronized fenofibrate in suspension, or by wet granulation of powder, according to which the constituents, including in particular the micronized fenofibrate, the surfactant and the cellulose derivative, are granulated by wet granulation using an aqueous wetting solution, dried and calibrated.

The pharmaceutical composition according to the present invention has a high proportion of fenofibrate; it may

therefore be provided in a formulation which is smaller in size than the formulations of the prior art, which makes this composition according to the invention easy to administer.

The amount of fenofibrate is greater than or equal to 60% by weight, preferably greater than or equal to 70% by weight, even more preferably greater than or equal to 75% by weight, relative to the weight of the composition.

In the context of the present invention, the fenofibrate is not comicronized with a surfactant. On the contrary, it is micronized alone and then combined with a surfactant and with the binding cellulose derivative, which is a solubilization adjuvant.

The surfactant is chosen from surfactants which are solid or liquid at room temperature, for example sodium lauryl sulfate, Polysorbate® 80 or Montane® 20, preferably sodium lauryl sulfate.

The fenofibrate/HPMC ratio is preferably between 5/1 and 15/1.

The surfactant represents between 1 and 10%, preferably between 3 and 5%, by weight relative to the weight of fenofibrate.

The binding cellulose derivative represents between 2 and 15%, preferably between 5 and 12%, by weight of the composition.

Hydroxypropylmethylcellulose is preferably chosen, the apparent viscosity of which is between 2.4 and 18 cP, and even more preferably between 2.4 and 3.6 cP, such as for example Pharmacoat 603®.

The mean size of the fenofibrate particles is less than 15 µm, preferably 10 µm, even more preferably less than 8 µm.

The composition of the invention may also contain at least one excipient such as diluents, for instance lactose, antifoaming agents, for instance Dimethicone® and Simethicone®, or lubricants, for instance talc.

The pharmaceutical composition of the invention advantageously consists of granules in an amount equivalent to a dose of fenofibrate of between 50 and 300 mg, preferably equal to 200 mg.

The present invention also relates to a method for preparing the powder or the granules, the composition of which is described above. This method uses no organic solvent.

According to a first variant, the granules are prepared by assembly on neutral microgranules.

The neutral microgranules have a particle size of between 200 and 1 000 microns, preferably between 400 and 600 microns.

The assembly is carried out in a sugar-coating pan, in a perforated coating pan or in a fluidized airbed, preferably in a fluidized airbed.

The assembly on neutral microgranules is carried out by spraying an aqueous solution containing the surfactant, the solubilized binding cellulose derivative, and the micronized fenofibrate in suspension.

According to a second variant, the granules are obtained by wet granulation of powder. The granulation enables the powders to be made dense and makes it possible to improve their flow properties. It also

allows better preservation of the homogeneity, by avoiding the various constituents becoming unmixed.

The micronized fenofibrate, the surfactant, the cellulose derivative and, optionally, the other excipients are mixed, granulated, dried and then calibrated. The wetting solution may be water or an aqueous solution containing the binding cellulose derivative and/or the surfactant.

According to a particular embodiment, the fenofibrate and the other excipients are mixed in a planetary mixer. The wetting solution is added directly to the mixture. The wet mass obtained is granulated with an oscillating granulator, and then dried in an oven. The granules are obtained after passage over an oscillating calibrator.

Figure 1 represents the in vivo release profile of the formulation of example 1C and of a formulation of the prior art in fasting individuals.

Figure 2 represents the in vivo release profile of the formulation of example 1C and of a formulation of the prior art in individuals who have just eaten.

Figure 3 represents the in vivo release profile of the formulation of example 2B and of a formulation of the prior art in fasting individuals.

Figure 4 represents the in vivo release profile of the formulation of comparative example 3 and of a formulation of the prior art in individuals who have just eaten.

The invention is illustrated in a nonlimiting way by the following examples.

Example 1: Granules

1A) Microgranules (XFEN 1735)

The microgranules are obtained by spraying an aqueous suspension onto neutral cores. The composition is given in the following table:

Formula	Amount (percentage by mass)
Micronized fenofibrate	64.5
Neutral microgranules	21
HPMC (Pharmacoat 603®)	11.2
Polysorbate® 80	3.3
Fenofibrate content	645 mg/g

The in vitro dissolution was determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The percentages of dissolved product as a function of time, in comparison with a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

Time (min)	15	30
Example 1A (% dissolved)	73	95
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formulation 1A dissolves more rapidly than Lipanthyl 200 M.

1B) Microgranules (X FEN 1935)

The mean size of the fenofibrate particles is equal to 6.9 ± 0.7 microns.

The microgranules are obtained by spraying an aqueous suspension onto neutral cores. The suspension contains micronized fenofibrate, sodium lauryl sulfate and HPMC.

The assembly is carried out in a Huttlin fluidized airbed (rotoprocess).

The formula obtained is given below.

FORMULA	AMOUNT (percentage by mass)
Micronized fenofibrate	65.2
Neutral microgranules	20.1
HPMC (Pharmacoat 603®)	11.4
Sodium lauryl sulfate	3.3
Fenofibrate content	652 mg/g

The size of the neutral microgranules is between 400 and 600 µm.

1C) <u>Gelatin capsules of microgranules (Y FEN 001)</u>

Microgranules having the following composition are prepared:

RAW MATERIALS	AMOUNT (percentage by mass)
Micronized fenofibrate	67.1
Neutral microgranules	17.2
Pharmacoat 603® (HPMC)	11.7
Sodium lauryl sulfate	3.3
35% dimethicone emulsion	0.2
Talc	0.5
Fenofibrate content	671 mg/g

according to the method described in paragraph 1A).

The microgranules obtained are distributed into size 1 gelatin capsules, each containing 200 mg of fenofibrate.

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The

comparative results with a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

Time (min)	15	30
Example 1C (% dissolved)	76	100
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formula 1C dissolves more rapidly than Lipanthyl 200 M.

The gelatin capsules are conserved for 6 months at 40°C/75% relative humidity. The granules are stable under these accelerated storage conditions. In vitro dissolution tests (in continuous flow cells with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N) were carried out. The percentages of dissolved product as a function of time for gelatin capsules conserved for 1, 3 and 6 months are given in the following table.

Dissolution time (min)	**Conservation time**		
	1 month (% dissolved product)	**3 months** (% dissolved product)	**6 months** (% dissolved product)
5	25.1	23.0	20.1
15	71.8	65.6	66.5
25	95.7	88.7	91.0
35	104.7	98.7	98.2
45	106.4	100.2	99.1
55	106.7	100.5	99.5
65	106.8	100.6	99.7

The evolution of the content of active principle during storage is given in the following table.

Content (mg/gelatin Capsule)	**Conservation time**			
	0	**1 month**	**3 months**	**6 months**
	208.6	192.6	190.8	211.7

Pharmacokinetic study carried out in fasting individuals

The in vivo release profile of the gelatin capsules containing the YFEN 01 granules at a dose of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 9 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and figure 1.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{0-t} (µg.h/ml)	76	119
AUC_{inf} (µg.h/ml)	96	137
C_{max} (µg/ml)	2.35	4.71
T_{max} (hours)	8.0	5.5
Ke (1/hour)	0.032	0.028
Elim ½ (hours)	26.7	24.9

The following abbreviations are used in the present application:

C_{max}: maximum concentration in the plasma,
T_{max}: time required to attain the Cmax,
$T_{1/2}$: plasmatic half-life,
AUC_{0-t}: area under the curve from 0 to t,
$AUC_{0-\infty}$: area under the curve from 0 to ∞,
Ke: Elimination constant.

The results obtained for Lipanthyl 200 M and for the product of example 1C are represented on figure 1 by curves 1 and 2, respectively.

These results show that the composition according to the present invention has a bioavailability which is greater than that of Lipanthyl 200 M in fasting individuals.

Pharmacokinetic study carried out in individuals who have just eaten

The in vivo release profile of the gelatin capsules containing the YFEN 01 granules at a dose of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 18 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and figure 2.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{0-t} (µg.h/ml)	244	257
AUC_{inf} (µg.h/ml)	255	270
C_{max} (µg/ml)	12	13
T_{max} (hours)	5.5	5.5
Ke (1/hour)	0.04	0.04
Elim ½ (hours)	19.6	19.3

The results obtained for Lipanthyl 200 M and for the product of example 1C are represented on figure 2 by curves 1 and 2, respectively.

These results show that the composition according to the present invention is bioequivalent to that of Lipanthyl 200 M in individuals who have just eaten.

Example 2: Powder

2A) Granules (X FEN 1992)

Granules having the following composition are prepared

FORMULA	PERCENTAGE BY MASS
Micronized fenofibrate	71
Lactose	21.5
HPMC (Pharmacoat 603®)	5
Sodium lauryl sulfate	2.5

The micronized fenofibrate, the HPMC and the lactose are mixed using a planetary mixer. This mixture is granulated in the presence of a solution of sodium lauryl sulfate.

The flow time of the granules is 7 s. The compacting capacity and the particle size distribution are given in the following tables. These measurements were carried out in accordance with the standards of the European Pharmacopoeia.

Compacting capacity (X FEN 1992)	
V0	204 ml
V10	186 ml
V500	168 ml
V1250	164 ml
V10-V500	22 ml

Particle size distribution (X FEN 1992)	
Sieve mesh size (mm)	**% of oversize mass**
0.6	8
0.5	9
0.355	12
0.2	30
0.1	23
0	18

2B) Gelatin capsules of granules (Y FEN 002)

- **Preparation**

The micronized fenofibrate is mixed in a PMA mixer (Niro Fielder) with lactose and HPMC, and then wetted with an aqueous solution of sodium lauryl sulfate. The mass obtained is granulated by passage over an oscillating granulator, dried and then calibrated on a sieve with a mesh size of 1.25 mm.

The granules are then packaged in size 1 gelatin capsules at doses of 200 mg of fenofibrate.

Granules of the following composition are obtained.

FORMULA	PERCENTAGE BY MASS
Micronized fenofibrate	70
Lactose	21.5
Pharmacoat 603® (HPMC)	5
Sodium lauryl sulfate	3.5
Content	700 mg/g

- **Properties of the granules**

The flow time of the granules is 6 s. The compacting capacity and the particle size distribution are given in the following tables. These measurements were

carried out in accordance with the standards of the European Pharmacopoeia.

Compacting capacity (Y FEN 002)	
V0	216 ml
V10	200 ml
V500	172 ml
V1250	170 ml
V10-V500	28 ml

Particle size distribution (Y FEN 002)	
Sieve mesh size (mm)	**% of oversize mass**
0.6	5
0.5	7
0.355	11
0.2	30
0.1	25
0	22

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results for a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

Time (min)	15	30
Example 2B (% dissolved)	82.2	88.5
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formulation 2B dissolves more rapidly than Lipanthyl 200 M.

- **Stability tests**

The gelatin capsules conserved at 40°C/75% relative humidity are stable for 6 months.

In vitro dissolution tests (in continuous flow cells with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N) were carried out. The percentages of dissolved product as a function of time for gelatin capsules conserved for 1, 3 and 6 months are given in the following table.

Dissolution time (min)	Conservation time		
	1 month (% dissolved product)	3 months (% dissolved product)	6 months (% dissolved product)
5	54.2	52.9	49.0
15	81.1	75.8	82.2
25	86.4	79.6	87.2
35	88.8	81.6	89.8
45	90.7	82.9	91.5
55	92.1	83.9	92.7
65	93.2	84.7	93.6

The evolution of the content of active principle during storage is given in the following table.

Content (mg/gelatin capsule)	Conservation time			
	0	1 month	3 months	6 months
	196.6	190.0	199.8	203.3

Pharmacokinetic study carried out in fasting individuals

The in vivo release profile of the gelatin capsules containing the YFEN 002 granules at doses of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 9 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and figure 3.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 2B
AUC_{0-t} (µg.h/ml)	76	70
AUC_{inf} (µg.h/ml)	96	82
C_{max} (µg/ml)	2.35	2.8
T_{max} (hours)	8.0	5.5
Ke (1/hour)	0.032	0.033
Elim ½ (hours)	26.7	23.1

The results obtained for Lipanthyl 200 M and for the product of example 2B are represented on figure 3 by curves 1 and 2, respectively.

These results show that the composition of example 2B is bioequivalent to that of Lipanthyl 200 M in fasting individuals.

Comparative example 3: batch ZEF 001

This example illustrates the prior art.

It combines micronization of fenofibrate and the use of a surfactant. It differs from the present invention by the use of the mixture of binding excipients consisting of a cellulose derivative other than HPMC: Avicel PH 101 and polyvinylpyrrolidone (PVP K30).

It is prepared by extrusion-spheronization.

- **Theoretical formula**

Products	Theoretical amount (%)
Micronized fenofibrate	75.08
Montanox 80®	4.72
Avicel PH 101®	5.02
PVP K 30®	4.12
Explotab®	11.06

- **In vitro dissolution profile**

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results with Lipanthyl 200 M are given in the following table.

Time (min)	15	30
Example 3 (% dissolved)	24	40
Lipanthyl 200 M (% dissolved)	47.3	64.7

The dissolution is slower than that observed for Lipanthyl 200 M.

Pharmacokinetic study carried out in fasting individuals

The in vivo release profile of the gelatin capsules containing the ZEF 001 granules at doses of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 5 fasting individuals receiving a single dose. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and figure 4.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 3
AUC_{0-t} (µg.h/ml)	92	47
AUC_{inf} (µg.h/ml)	104	53
C_{max} (µg/ml)	3.5	1.7
T_{max} (hours)	5.6	4.6
Ke (1/hour)	0.04	0.038
Elim ½ (hours)	18.9	20.3

The results obtained for Lipanthyl 200 M and for the product of example 3 are represented on figure 4 by curves 1 and 2, respectively.

These results show the greater bioavailability of Lipanthyl 200 M compared with this formulation based on the prior art.

Example 3 shows that combining the knowledge of the prior art (namely micronization or use of surfactants) does not make it possible to obtain rapid dissolution of fenofibrate. This results in low bioavailability compared with Lipanthyl 200 M.

The compositions prepared according to the present invention show more rapid dissolution than the formula of the prior art and improved bioavailability.

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JC13 Rec'd PCT/PTO 08 JAN 2002

CLAIMS

1. A pharmaceutical composition containing micronized fenofibrate, a surfactant and a binding cellulose derivative as a solubilization adjuvant, characterized in that it contains an amount of fenofibrate greater than or equal to 60% by weight.

2. The composition as claimed in claim 1, characterized in that the binding cellulose derivative, which is a solubilization adjuvant, is hydroxypropylmethylcellulose.

3. The composition as claimed in claim 2, characterized in that the hydroxypropylmethyl-cellulose has an apparent viscosity of between 2.4 and 18 cP, preferably of between 2.4 and 3.6 cP.

4. The composition as claimed in one of claims 1 to 3, characterized in that it contains an amount of fenofibrate, greater than or equal to 70% by weight, even more preferably greater than or equal to 75% by weight, relative to the weight of the composition.

5. The composition as claimed in one of the preceding claims, characterized in that the surfactant is chosen from the group made up of polysorbate® 80, Montane® 20 and sodium lauryl sulfate.

6. The composition as claimed in one of the preceding claims, characterized in that the surfactant represents between 1 and 10%, preferably between 3 and 5%, by weight relative to the weight of the fenofibrate.

7. The composition as claimed in one of claims 2 to 6, characterized in that the fenofibrate/HPMC mass ratio is between 5/1 and 15/1.

8. The composition as claimed in one of the preceding claims, characterized in that the binding cellulose derivative represents between 2 and 15%, preferably between 5 and 12%, by weight of the composition.

9. The composition as claimed in one of the preceding claims, characterized in that it contains at least one excipient such as a diluent, for instance lactose, an antifoaming agent, for instance Dimethicone® or Simethicone®, or a lubricant, for instance talc.

10. The composition as claimed in one of the preceding claims, characterized in that the mean size of the fenofibrate particles is less than 15 µm, preferably less than 8 µm.

11. The composition as claimed in one of the preceding claims, characterized in that it is in the form of gelatin capsules containing powder or granules.

12. A method for preparing the composition as claimed in one of the preceding claims, characterized in that granules are prepared by assembly on neutral microgranules, by spraying an aqueous suspension containing the surfactant, the solubilized binding cellulose derivative and the micronized fenofibrate in suspension.

13. The method for preparing the composition as claimed in one of claims 1 to 11, characterized in that granules are obtained by wet granulation of powder, according to which the constituents, including in

constituents, including in particular the micronized fenofibrate, the surfactant and the cellulose derivative, are granulated by wet granulation using an aqueous wetting solution, dried and calibrated.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

WIPO

PCT

(43) International publication date
18 January 2001 (18.01.2001)

(10) International publication number
WO 01/03693 A1

(51) International patent classification[7]: A61K 31/216, 9/16

(21) International application number: PCT/FR00/01971

(22) International filing date: 7 July 2000 (07.07.2000)

(25) Language of filing: French

(26) Language of publication: French

(30) Data relating to the priority:
99/08,923 9 July 1999 (09.07.1999) FR

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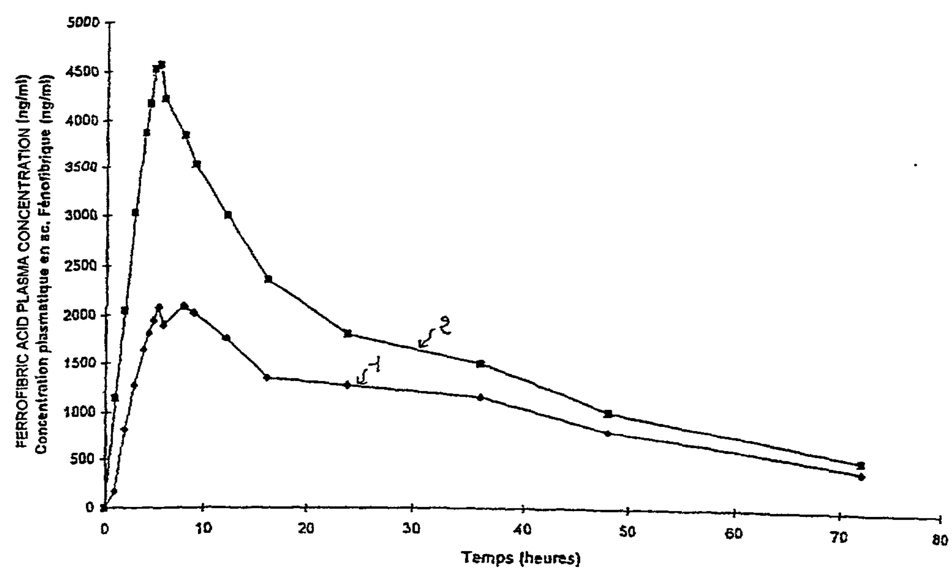
[continued on next page]

As printed

(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND PREPARATION METHOD

(54) Titre: COMPOSITION PHARMACEUTIQUE CONTENANT DU FENOFIBRATE ET PROCEDE DE PREPARATION



(57) Abstract: The invention concerns a pharmaceutical composition containing micronized fenofibrate, a surfactant and a binding cellulose derivative, as solubilizing adjuvant, preferably hydroxypropylmethylcellulose. The cellulose derivative represents less than 20 wt. % of the composition. The association of micronized fenofibrate with a binding cellulose derivative, as solubilizing adjuvant and a surfactant enables to enhance the bioavailability of the active principle. The invention also concerns a method for preparing said composition without using any organic solvent.

[continued on next page]

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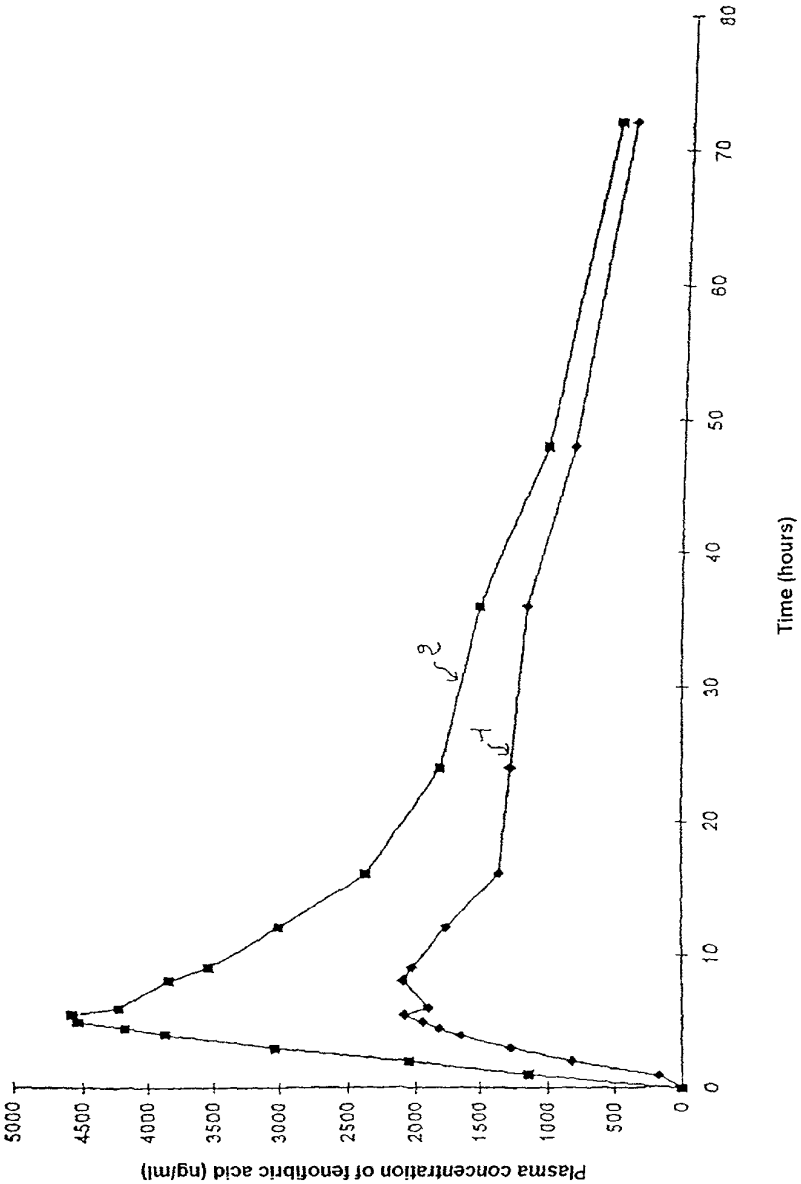
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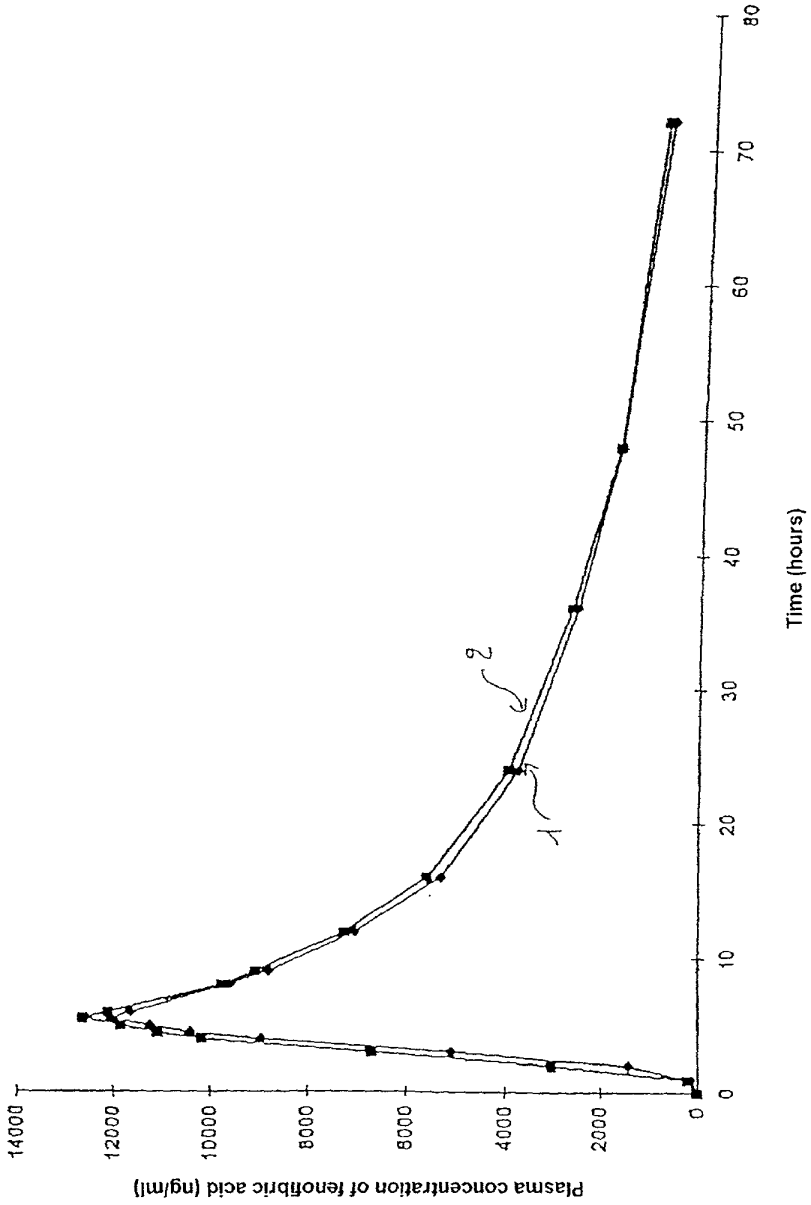
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
70
80
Time (hours)
2
1

Figure 1

Figure 2


Plasma concentration of fenofibric acid (ng/ml)
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12000
10000
8000
6000
4000
2000
0
0
10
20
30
40
50
60
70
80
Time (hours)
1
2

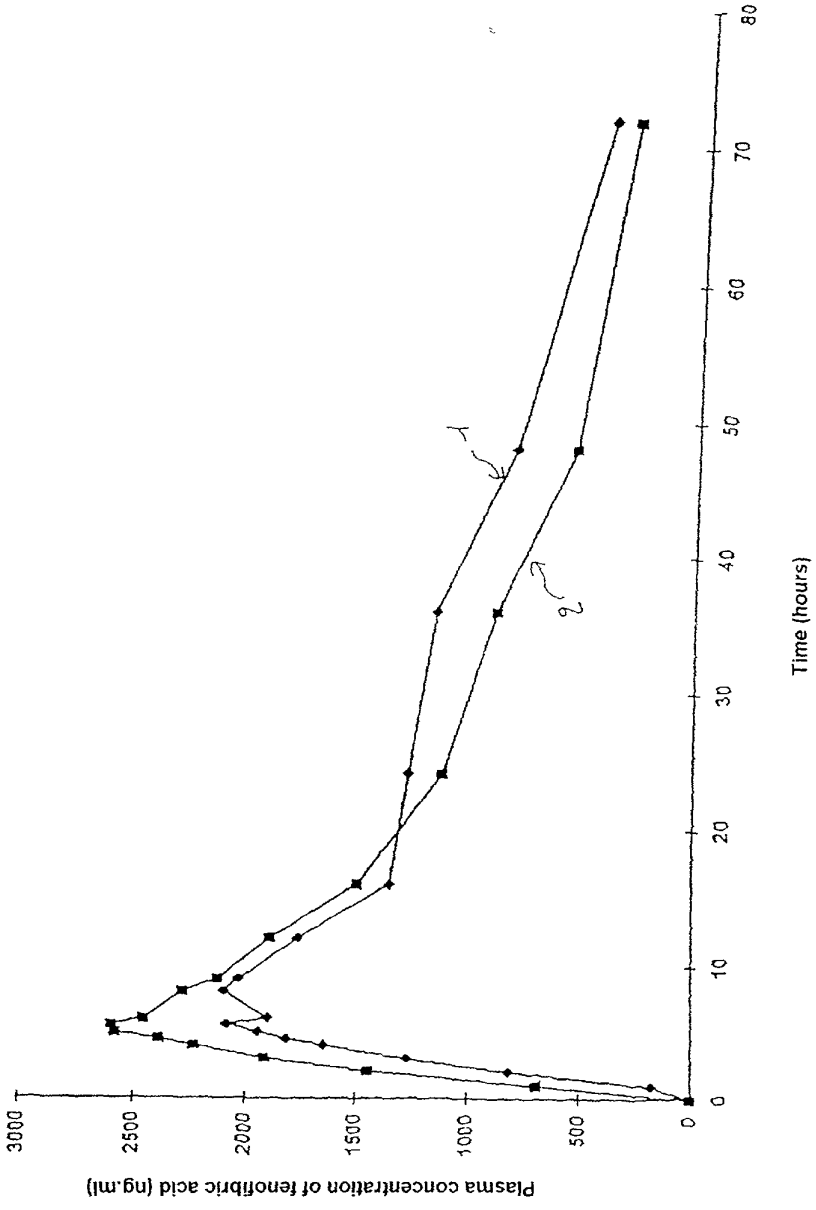
Plasma concentration of fenofibric acid (ng.ml)
3000
2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
70
80
Time (hours)
1
2

Figure 3

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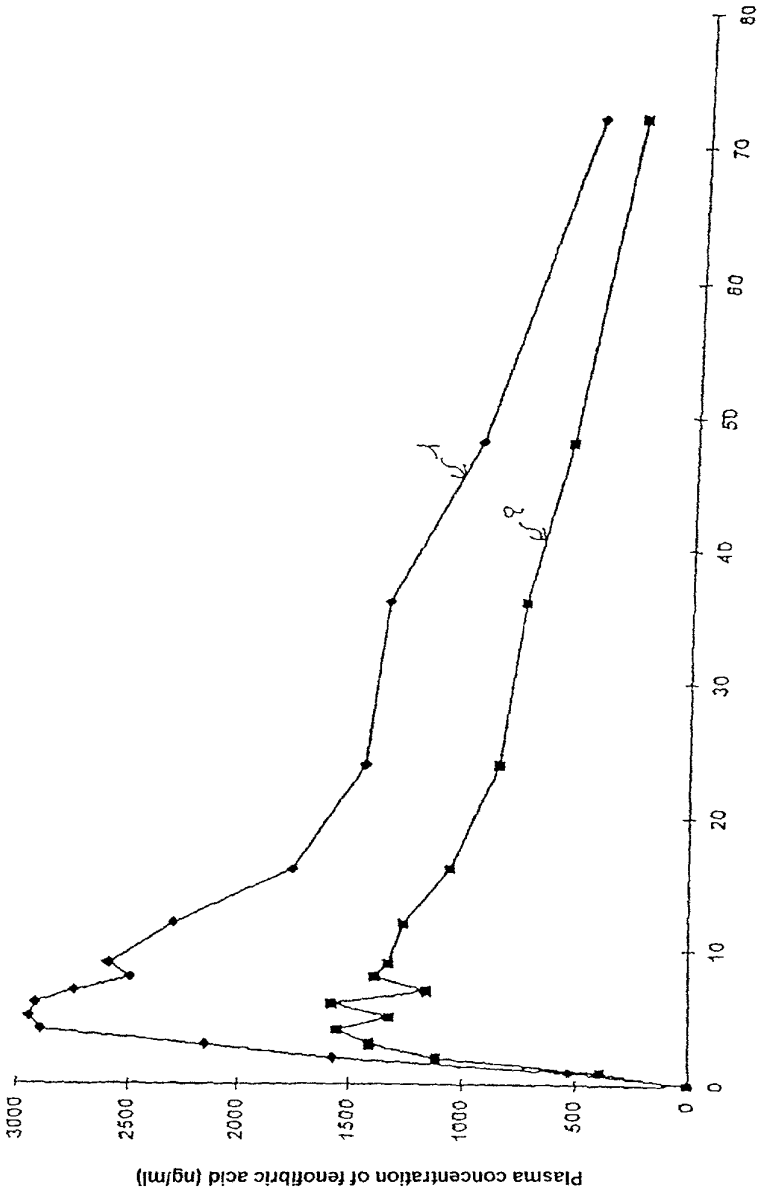
Figure 4



#5

Attorney Docket No. _____

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: Pharmaceutical composition containing fenofibrate and method for the preparation thereof the specification of which ☐ is attached and/or ☒ was filed on JULY 7, 2000 as ~~United States Application Serial No.~~ _____ or PCT International Application No. PCT/FR00/01971 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate or § 365(a) of any PCT international application(s) designating at least one country other than the United States, listed below and have also identified below, any foreign application(s) for patent or inventor's certificate, or any PCT international application(s) having a filing date before that of the application(s) of which priority is claimed:

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C.
FRANCE	99/08923	JULY 9, 1999	☒ YES ☐ NO
			☐ YES ☐ NO

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Application Number	Date of Filing

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT International filing date of this application:

Application Number	Date of Filing	Status (Patented, Pending, Abandoned)
PCT/FR00/01971	JULY 7, 2000	Pending

I hereby appoint the following attorney and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 20,630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 20,645; Jerry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No. 20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Larry O'Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, Reg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; Robert D. Bajefsky, Reg. No. 25,387; Richard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. Lipsey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewris, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, Reg. No. 30,413; Roger D. Taylor, Reg. No. 28,992; David M. Kelly, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Y. Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg. No. 32,095; Jean B. Fordis, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,120; James K. Hammond, Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,824; Thomas W. Banks, Reg. No. 32,719; Christopher P. Isaac, Reg. No. 32,616; Bryan C. Diner, Reg. No. 32,409; M. Paul Barker, Reg. No. 32,013; Andrew Chanho Sonu, Reg. No. 33,457; David S. Forman, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 32,867; James W. Edmondson, Reg. No. 33,871; Michael R. McGurk, Reg. No. 32,045; Joann M. Neth, Reg. No. 36,363; Gerson S. Panitch, Reg. No. 33,751; Cheri M. Taylor, Reg. No. 33,216; Charles E. Van Horn, Reg. No. 40,266; Linda A. Wadler, Reg. No. 33,218; Jeffrey A. Berkowitz, Reg. No. 36,743; Michael R. Kelly, Reg. No. 33,921; James B. Monroe, Reg. No. 33,971; Doris Johnson Hines, Reg. No. 34,629; Allen R. Jensen, Reg. No. 28,224; Lori Ann Johnson, Reg. No. 34,498; and David A. Manspeizer, Reg. No. 37,540 and _____. Please address all correspondence to FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P. 1300 I Street, N.W., Washington, D.C. 20005, Telephone No. (202) 408-4000.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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2-00

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Post Office Address		
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Residence		Citizenship
Post Office Address		
Full Name of Sixth Inventor	Inventor's Signature	Date
Residence		Citizenship
Post Office Address		
Full Name of Seventh Inventor	Inventor's Signature	Date
Residence		Citizenship
Post Office Address		
Full Name of Eighth Inventor	Inventor's Signature	Date
Residence		Citizenship
Post Office Address		
Full Name of Ninth Inventor	Inventor's Signature	Date
Residence		Citizenship
Post Office Address		

Listing of Inventors Continued on Page 2 hereof. ☐ Yes ☐ No